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Per our conversation, a fax copy of the FA for 10/615560. Please give me a call if you have any questions. Thanks Katherine Salmon

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DETAILED ACTION

1. This action is in response to papers filed 3/16/2006.

2. Claims 1-17 are under consideration at this time.

3. The following objections and rejections are either newly applied or are reiterated. Response to arguments follows.

Withdrawn Objections and Rejections

4. The objection to the drawings, made at Section 1 of the previous office action, is moot in view of the replacement of the drawings.

5. The objection to the specification, made at Section 2 of the previous office action, is moot in view of the amendment specification.

6. The rejection of Claim 12 under 35 U.S.C. 112, second paragraph, made at section 3 of the previous office action, is moot in view of the argument that heavy atoms for labeling would be known by one of ordinary skill (p. 8 of the reply).

7. The rejection of Claims 1, 2, 8-9, 11-13 under 35 U.S.C. 102(b), as anticipated by Takahagi et al. in the previous office action, is moot in view of the amendment to the claims of a microarray by spatially directed synthesis.

8. The rejection of Claims 1, 8-9, and 12-14 under 35 U.S.C. 102(b), as anticipated by Hermann et al. in the previous office action, is moot in view of the amendment to the claims of a microarray by spatially directed synthesis.

9. The rejection of Claims 1, 8, and 4-6 under 35 U.S.C. 102(b), as anticipated by Walt et al. in the previous office action, is moot in view of the amendment to the claims of a microarray by spatially directed synthesis.

10. The rejection of Claims of Claims 15-17 under 35 U.S.C. 103(a), made at section 9 of the previous office action, is moot in view of the traversal on the grounds that Seiko Epson Corporation (JP 2001-176941 6/29/2001) does not teach testing the microarray under two conditions.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "at least about" because the metes and bounds of the invention are not clear. As the CAFC noted, and affirmed, regarding the district court determination of this phrase in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016 at page 1031 "the court held the "at least about" claims to be invalid for indefiniteness." The claims are indefinite with regard to the values encompassed.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-2, 8-9, 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Taton et al. (Science September 8, 2000 Vol. 289).

Taton et al. teaches a method for analyzing combinatorial DNA arrays using oligonucleotide-modified gold nanoparticle probes (Abstract). With regard to Claims 1 and 9, Taton et al. teaches synthesizing oligomers on an array by spotting an array with various oligonucleotides (spatially directed synthesis) (Scheme 1 p. 1757 and p. 1758 1st paragraph). Taton et al. teaches using a SEM to detect the target and probe (supplemental Figure 2). With regard to Claims 2 and 11, Taton et al. teaches the use of a DNA array (nucleotides, oligonucleotides, or polynucleotides (Abstract). With regard to Claim 8, Taton et al. teaches the use of gold nanoparticles modified with oligonucleotides attached to the chip (a chip coated with a layer of metals) (p. 1757 last paragraph). With regard to Claims 11-12, Taton et al. teaches the use of gold oligonucleotides (heavy atoms) which are enhanced with a silver material at the surface (p. 1758 1st column).

13. Claims 1-3, and 8-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Park et al. (Science February 2002 Vol. 295 p. 1503).

Park et al. teaches a method of detection using oligonucleotides functionalized with gold nanoparticles (Abstract). With regard to Claim 1-3,and 9-11, Park et al. teaches an array was designed on a Si wafer by standard photolithography (light directed synthesis) (p. 1504 1st column 1st full paragraph). Park et al. teaches the microarray was scanned to detect the oligonucleotides (Figure 3 p. 1505). With regard to Claims 8 and 12, Park et al. teaches the array is covered with gold nanoparticles

(heavy atoms) and silver deposition (coated in a layer of metals) (Abstract). Park et al. teaches the array is treated with a silver enhancer solution (p. 1504 1st column last paragraph). Park et al. teaches scanning a microarray (with attached biomolecules) before silver deposition, after a 3-minute treatment of silver enhancer solution, after a 6-minute treatment of silver enhancer solution, and after a 9-minute treatment of silver enhancer solution.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-5, 8-13 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGall et al. (US Patent 5,843,655 December 1, 1998) in view of

Takahagi, et al. (Scanning Electron Microscope Observation of Heterogeneous Three-Dimensional Arrays using DNA May 15 2001 Japanese Journal of Applied Physics, Part 2: Letters p. L521-L523)

McGall et al. teaches an oligonucleotide array which is synthesized by light directed oligonucleotide synthesis (Claims 1-3 and 9-11 and 16-17) (see column 3, lines 37-38 and Figure 2). Claim 4 is drawn to scanning a microarray to detect errors in synthesizing. McGall et al. teaches providing a substrate which has two ensembles of different sequence specific oligonucleotides have been synthesized by spatially directed oligonucleotide synthesis (see Column 9, lines 15-20). McGall et al. teaches that these two ensembles are exposed to the same test conditions (see Column 9, line 21). McGall teaches test conditions (for example, chemical reagents, exposure to light, acid agent, reducing agent) can be used to test for deprotection (see Column 9, lines 23-25). Detection of testing conditions having an impact on deprotection of the oligonucleotide would show errors between one set of arrays and another. Claim 5 is drawn to detecting a misalignment of the plurality of biomolecules. McGall et al. teaches that biological chips have been produced in which each location has a scale of 10 microns (see column 1, line 23-25). With regard to claim 8 McGall et al. teaches that the surface of the solid substrate may be composed of metals (see column 14, lines 33-38).

With regard to Claim 15, McGall et al. teaches a novel method for identifying production parameters in the synthesis of oligonucleotide arrays (Column 15 lines 15-18). McGall et al. teaches that under selected test conditions, scanning devices can examine each location in the array and determine whether a target molecule has

interacted with the probe at that location (see column 1, lines 26-30). McGall teaches test conditions (for example, chemical reagents, exposure to light, acid agent, reducing agent) can be used to test for deprotection (see Column 9, lines 23-25). McGall et al. teaches that one method involves determining the extent to which a test condition causes the appearance of a structural feature in oligonucleotides produced on an array (Column 1, lines 58-60). McGall et al. teaches a method to test a variety of combinations of conditions on a single chip as quality control procedure for manufacturing oligonucleotide arrays (Column 4, lines 24-27). McGall et al. teaches a method of exposing a chip to one or more test conditions throughout the chip productions process and changing test conditions during the production process (Column 11, lines 20-30). McGall et al. teaches identifying the effect of a condition on the manufacturing process and determining the effect at each area (Column 11, lines 33-34 and 51). Therefore, McGall et al. teaches testing two test conditions in a manufacturing process in order to identify production parameters (select conditions for manufacturing).

McGall et al., however, does not teach using a SEM to detect changes in microarrays.

Takahagi et al. teaches using a SEM to detect the construction of a nanostructure (an array) (see p. L521 last paragraph). Takahagi et al. teaches a fabricating method for a heterogeneous three-dimensional nanoparticle array composed of gold nanoparticles lined by thiol-synthesized DNA oligonucleotide. Takahagi et al. teaches a hybridized solution of DNA (oligonucleotides) and gold (p. L521 2nd column

1st paragraph) (Claims 1 and 2). Takahagi et al teaches placing a droplet of the hybridized solution onto a silicon substrate (array) (Claim 8 array coated in metal) (p. L521 last paragraph). Takahagi et al. teaches using a SEM to provide visual evidence of the construction of a nanostructure (p. L521 last paragraph). Takayuki et al. teaches that 2 sizes of gold particles (20nm and 9nm) each covered with heptanethiol are mixed together (Figure 1 page L522). The two gold particles are mixed in a hybridization condition (P. L521 2nd paragraph 2nd column). Takayuki et al teaches that a droplet of the hybridized solution comprising a biomolecule probe was cast onto a substrate (p. L521 last paragraph). Takayuki teaches the two gold particles are attached to the substrate are still in a hybridize solution (p. L521 last paragraph). The molecules are then scanned using SEM to detect binding (p. L521 last paragraph). Takahagi et al. teaches the gold particle is hybridized to an oligonucleotide (Figure 1 p. L522). Takahagi teaches an aqueous colloidal gold (Ag) solution containing nanoparticles of 9 nm and 20 nm (Claim 13) (P. L521 1st paragraph 2nd column). The claims and the specification fail to define the phrase "heavy atom". In the instant case, a heavy atom will be defined as gold. Takahagi et al. teaches that the two gold particles hybridize together (Claim 12) (Figure 1 p. L522).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of McGall et al. by including the use of a SEM as taught by Takahagi et al. The ordinary artisan would be motivated to improve the method of McGall et al., by including the use of a SEM, because Takahagi et al. teaches that using a SEM provides a visual evidence of the

construction of a nanostructure (L521 last paragraph). McGall et al. teaches an array in which each individual location of the array is on a scale of 10 microns. The ordinary artisan would have been motivated to observe the individual components of a specific location on the array.

Response to Arguments

The response traverses the rejection. The response asserts that none of the references used in the 103 rejection teach "scanning said microarray with a scanning electron microscope". The response further asserts that Takahagi fails to suggest a microarray or the analysis of a microarray (p. 14). This argument has been reviewed but is not convincing because the combination of the two references cited above make the instant claim invention obvious. McGall et al. teaches that under selected test conditions, scanning devices can examine each location in the array and determine whether a target molecule has interacted with the probe at that location (see column 1, lines 26-30). A scanning device, therefore, can be used to scan an array for probe-target hybridization. Takahai et al teaches analyzing a hybridized solution on a slide. It would be obvious to use the SEM technique taught by Takahai et al in the method of McGall et al because in both instances the ordinary user would be scanning a slide.

15. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGall et al. (US Patent 5,843,655 December 1, 1998) in view of Takahagi, et al. (Scanning Electron Microscope Observation of Heterogeneous Three-Dimensional

Arrays using DNA May 15 2001 Japanese Journal of Applied Physics, Part 2: Letters p. L521-L523) and McMullan (Scanning Electron Microscopy. 51st Annual Meeting of the Microscopy Society of America, Cincinnati, August 1993. www-g.eng.cam.ac.uk/125/achievements/semhist-intro.com)

Neither McGall et al. or Takahagi et al. teach the resolution size of less than about 5 micron and less than about 1 micron.

McMullan teaches the history of the SEM and the standard resolutions for the microscopes. With regard to Claims 6-7, McMullan teaches that marketed microanalysers (SEM) by 1965 had the resolution of 1 micron (see p. 13 McMullan).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to use a resolution size of less than 5 micron and less than 1 micron as taught by McMullan in the method of McGall et al. and Takahagi et al. The ordinary artisan would have been motivated to detect resolutions size of less than 5 micron and less than 1 micron because McMullan teaches that SEMs have the capability of observing areas as small as 1 micron. The ordinary artisan would have been motivated to detect errors using a commercial SEM with small resolution in order to be able to synthesis arrays in which many biomolecules can be synthesized on a small-scale chip.

16. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over McGall et al. (US Patent 5,843,655 December 1, 1998) in view of Takahagi, et al. (Scanning Electron Microscope Observation of Heterogeneous Three-Dimensional Arrays using

DNA May 15 2001 Japanese Journal of Applied Physics, Part 2: Letters p. L521-L523) and Hermann et al. (Histochem Cell Biol 1996 Vol. 106 p. 31).

Neither McGall et al. or Takahagi et al. teach the measuring with a secondary electron detector or a backscattered electron detector.

Hermann et al. teaches a method of scanning with a scanning electron microscope a gold-labeled biological surface (Figure 1). With regard to Claim 14, Hermann et al. teaches using a backscattered electron signal (BSE) to detect unambiguously localized colloidal gold and to detect a size of 5nm and ultra small gold colloids to a size of 1nm(p. 32 1st column 1st paragraph and 2nd paragraph).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of McGall et al. and Takahagi et al. by detecting using a backscattered electron detector as taught by Hermann et al. The ordinary artisan would be motivated to improve the method of McGall et al. and Takahagi et al., by detecting using a backscattered electron detector, because Hermann et al. teaches that BSE detects a signal produced by small colloidal gold particles and has high sensitivity and fast response (p. 32 1st column 1st full paragraph). The ordinary artisan would to use a BSE in order to quickly detect the small gold particles, which would enable the user to make small high-density arrays that can be quickly scanned for detection of hybridization.

17. Claims 3 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taton et al. (Science September 8, 2000 Vol. 289) in view of McGall et al. (US Patent 5,843,655 December 1, 1998).

Taton et al. teaches a method for analyzing combinatorial DNA arrays using oligonucleotide-modified gold nanoparticle probes (Abstract). With regard to Claims 1 and 9, Taton et al. teaches synthesizing oligomers on an array by spotting an array with various oligonucleotides (spatially directed synthesis) (Scheme 1 p. 1757 and p. 1758 1st paragraph). Taton et al. teaches using a SEM to detect the target and probe (supplemental Figure 2).

Taton et al., however, does not teach synthesizing by light directed oligonucleotide synthesis.

McGall et al. teaches an oligonucleotide array which is synthesized by light directed oligonucleotide synthesis (see column 3, lines 37-38 and Figure 2). McGall et al. teaches that under selected test conditions, scanning devices can examine each location in the array and determine whether a target molecule has interacted with the probe at that location (see column 1, lines 26-30).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Taton et al. by including synthesizing by light directed oligonucleotide synthesis as taught by McGall et al. The ordinary artisan would be motivated to improve the method of Taton et al., by synthesizing by light directed oligonucleotide synthesis, because McGall et al. teaches a synthesizing method which using photolithography and the process can be miniaturized

to generate high-density arrays of oligonucleotide probes (Column 5, lines 5-10). The ordinary artisan would want to use a synthesizing method which generates high-density arrays in order to be able to test as many probe-target interactions as possible simultaneously.

18. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taton et al. (Science September 8, 2000 Vol. 289) in view of Hermann et al. (Histochem Cell Biol 1996 Vol. 106 p. 31).

Taton et al. teaches a method for analyzing combinatorial DNA arrays using oligonucleotide-modified gold nanoparticle probes (Abstract). Taton et al. teaches synthesizing oligomers on an array by spotting an array with various oligonucleotides (spatially directed synthesis) (Scheme 1 p. 1757 and p. 1758 1st paragraph). Taton et al. teaches using a SEM to detect the target and probe (supplemental Figure 2).

Taton et al., however, does not teach a method of detecting using a backscattered electron detector.

Hermann et al. teaches a method of scanning with a scanning electron microscope a gold-labeled biological surface (Figure 1). With regard to Claim 14, Hermann et al. teaches using a backscattered electron signal (BSE) to detect unambiguously localized colloidal gold and to detect a size of 5nm and ultra small gold colloids to a size of 1nm (p. 32 1st column 1st paragraph and 2nd paragraph).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Taton et al. by detecting using a backscattered electron detector as taught by Hermann et al. The

ordinary artisan would be motivated to improve the method of Taton et al., by detecting using a backscattered electron detector, because Hermann et al. teaches that BSE detects a signal produced by small colloidal gold particles and has high sensitivity and fast response (p. 32 1st column 1st full paragraph). The ordinary artisan would to use a BSE in order to quickly detect the small gold particles which would enable the user to make small high-density arrays that can be quickly scanned for detection of hybridization.

19. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. (Science February 2002 Vol. 295 p. 1503) in view of Hermann et al. (Histochem Cell Biol 1996 Vol. 106 p. 31).

Park et al. teaches a method of detection using oligonucleotides functionalized with gold nanoparticles (Abstract). Park et al. teaches an array was designed on a Si wafer by standard photolithography (light directed synthesis) (p. 1504 1st column 1st full paragraph). Park et al. teaches the microarray was scanned to detect the oligonucleotides (Figure 3 p. 1505).

Park et al., however, does not teach a method of detecting using a backscattered electron detector.

Hermann et al. teaches a method of scanning with a scanning electron microscope a gold-labeled biological surface (Figure 1). With regard to Claim 14, Hermann et al. teaches using a backscattered electron signal (BSE) to detect

unambiguously localized colloidal gold and to detect a size of 5nm and ultra small gold colloids to a size of 1nm(p. 32 1st column 1st paragraph and 2nd paragraph).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Park et al. by detecting using a backscattered electron detector as taught by Hermann et al. The ordinary artisan would be motivated to improve the method of Park et al., by detecting using a backscattered electron detector, because Hermann et al. teaches that BSE detects a signal produced by small colloidal gold particles and has high sensitivity and fast response (p. 32 1st column 1st full paragraph). The ordinary artisan would to use a BSE in order to quickly detect the small gold particles, which would enable the user to make small high-density arrays that can be quickly scanned for detection of hybridization.

Double Patenting

20. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

21. Claims 1-13 and 15-17 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12, 16, and 18-20 of copending

Application No. 10/835434. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claim 14 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 17 of copending Application No. 10/835434. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 14 of the instant application is generic to all that is recited in Claim 17 of U.S. Application No. 10/835,434. That is, Claim 17 of '434 falls entirely within the scope of Claim 14, or in other words, Claim 14 is anticipated by Claim 17 of '434. Claim 17 of U.S. Application No. 10/835,434 recites a method where a heavy atom which was enhanced was detected by backscattered electron detector. The instant application's Claim 14 is drawn more broadly to detecting any atom using backscattered electron detector. Thus, Claim 17 of '434 is encompassed by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

The response acknowledges the Double patenting rejection and will consider canceling and/or amending the conflicting claims in copending US Application 10/835434 and filing a Terminal Disclaimer when the pending claims are otherwise allowable. The rejection will be maintained until this has been done.

Conclusion

24. No claims are allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634